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(71) Applicant : **Ajinomoto Co., Inc.**
No. 15-1, Kyobashi 1-chome
Chuo-ku
Tokyo (JP)

(72) Inventor : **Ohsumi, Koji c/o Centr. Research Lab.**
Ajinomoto Co., Inc.
No. 1-1 Suzuki-cho
Kawasaki-ku Kawasaki-shi Kanagawa-ken (JP)

Inventor : **Tsuji, Takashi c/o Centr. Research Lab.**
Ajinomoto Co., Inc.
No. 1-1 Suzuki-cho
Kawasaki-ku Kawasaki-shi Kanagawa-ken (JP)

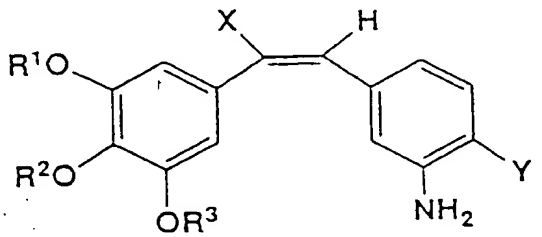
Inventor : **Morinaga, Yoshihiro c/o Centr. Research Lab.**
Ajinomoto Co., Inc.
No. 1-1 Suzuki-cho
Kawasaki-ku Kawasaki-shi Kanagawa-ken (JP)

Inventor : **Ohishi, Kazuo c/o Centr. Research Lab.**
Ajinomoto Co., Inc.
No. 1-1 Suzuki-cho
Kawasaki-ku Kawasaki-shi Kanagawa-ken (JP)

(74) Representative : **Nicholls, Kathryn Margaret et al**
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

(54) Cytotoxic stilbene derivatives and pharmaceutical composition containing them.

(57) Stilbene derivatives of the following general formula (1) or their pharmaceutically acceptable acid addition salts are low in toxicity, but are water soluble and effective as carcinostatics :



(1)

wherein R^1, R^2 and R^3 each represent an alkyl group having 1 to 3 carbon atoms ; X represents a hydrogen atom or a nitrile group ; and Y represents an alkyloxy group having 1 to 3 carbon atoms, an alkyl group having 1 to 6 carbon atoms or a halogen atom.

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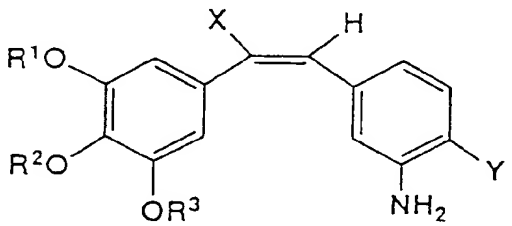
The present invention relates to cis-stilbene derivatives, to their use as pharmaceuticals and, in particular, to carcinostatics containing them as active ingredients.

Combretastatins having cis-stilbene as their basic skeleton are known to have strong cytotoxicity. However, because they are barely soluble in water, they have not been put to practical use as medicines. Therefore, various investigations to develop their derivatives have been made (Molecular Pharmacology 34, 200-206 (1988); J. Med. Chem., 34, 2579-2588(1991); WO 92/16486; J. Med. Chem., 35, 2293-2306(1992); WO 93/23357; J. Med. Chem., 36, 2817-2821(1993); Bioorg. Med. Chem. Let., 4, 699-704(1994)), but compounds-,which are effective in vivo are still unknown.

The present inventors sought to identify combretastatin derivatives which may be synthesized easily, which are of low toxicity and which have a high pharmaceutical effect, and to provide carcinostatics containing them.

The present inventors synthesized various stilbene derivatives and screened carcinostatic compounds from them and, as a result, found that compounds of the following general formula (1) have a remarkable carcinostatic effect in vivo.

These compounds, which have an amino group at the 3-position of the benzene ring of cis-stilbene, are novel combretastatin derivatives.



(1)

wherein R^1, R^2 and R^3 each represent an alkyl group having 1 to 3 carbon atoms; X represents a hydrogen atom or a nitrile group; Y represents an alkyloxy group having 1 to 3 carbon atoms, an alkyl group having 1 to 6 carbon atoms or a halogen atom.

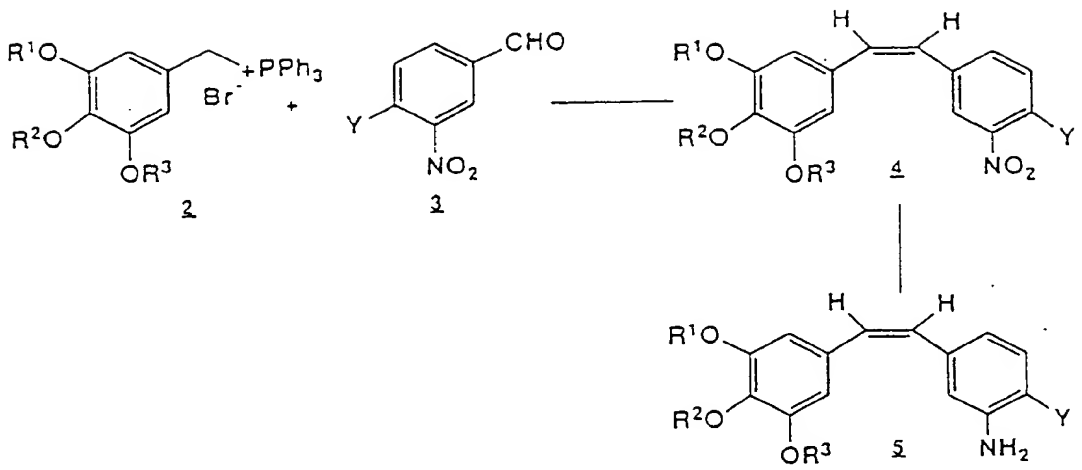
In formula (1), the term "alkyl groups having 1 to 3 carbon atoms" means methyl, ethyl or propyl; the term "alkyl groups having 1 to 6 carbon atoms" means methyl,ethyl, propyl, iso-propyl, butyl, iso-butyl, pentyl, hexyl and the like; the term "halogen atoms" means fluorine atom, chlorine atom, bromine atom and iodine atom.

In preferred compounds R^1, R^2 and R^3 are all methyl groups. Y is most preferably a methoxy group

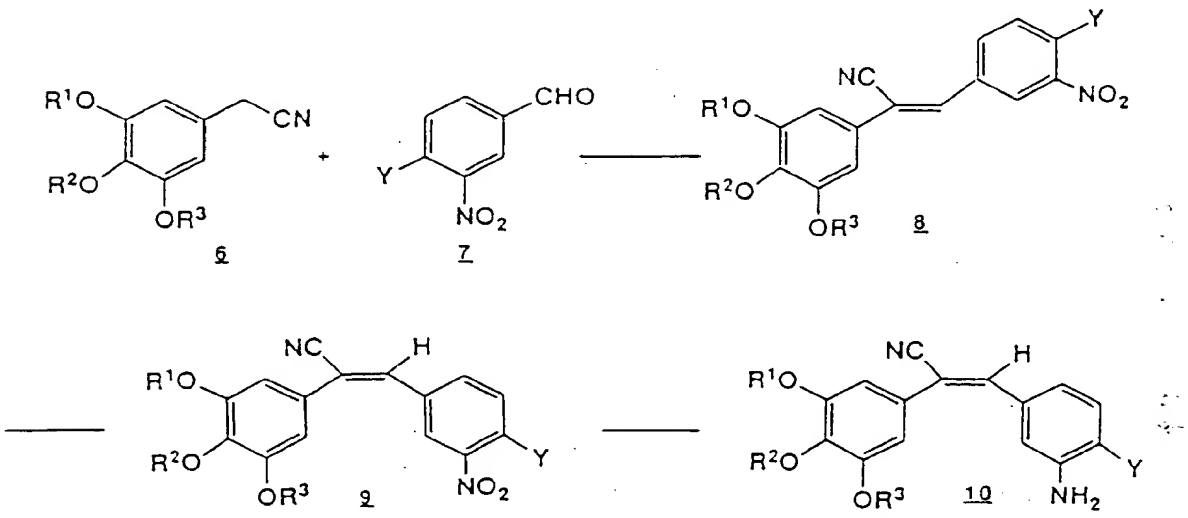
Such compounds include, for example, the following:

(Z)-1-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene,
(Z)-1-(3-amino-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene,
(Z)-1-(3-amino-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene,
(E)-3-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-en-nitrile,
(E)-3-(3-amino-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-en-nitrile,
(E)-3-(3-amino-4-methyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-en-nitrile.

Compounds of formula (1) of the present invention may be produced, for example, according to the reaction route mentioned below.



In these formulae, R^1, R^2, R^3 and Y have the same meanings as those mentioned above.



In these formulae, R^1, R^2, R^3 and Y have the same meanings as those mentioned above.

Precisely, compounds of formula (5) which belong to the compounds of the present invention may be obtained, for example, by reacting a triphenylphosphine bromide derivative of formula (2) and an aldehyde of formula (3) at room temperature in alcohol or benzene, etc. in the presence of a base such as sodium hydride or sodium ethoxide for 2 to 4 hours followed by subjecting the reaction product to chromatography, etc. to obtain the intended cis-compound. The cis-compound may be reduced with zinc-acetic acid or the like to obtain a compound of formula (5).

Compounds of formula (10) which belong to the compounds of the present invention may be produced, for example, by reacting a phenylacetonitrile derivative (6) and an aldehyde derivative (7) in dichloromethane, etc. in the presence of sodium hydroxide for 2 to 4 hours, obtaining the cis-compound (9) by photo-isomerising the trans-compound (8) followed by reducing the cis-compound (9) with a reducing agent such as zinc-acetic acid.

The stilbene derivatives of the present invention that have been produced according to the above-mentioned method may easily be separated and purified from the reaction mixtures by ordinary isolating and purifying means, for example, by extraction with solvents, chromatography, crystallization, etc.

Where the above-mentioned stilbene derivatives are used as carcinostatics, they are administered to patients perorally or parenterally (for example, by intramuscular injection, subcutaneous injection or intravenous injection or as suppositories, etc.). Their dose varies, depending on the symptoms of patients. In general, it may be from 1 to 9000 mg/adult/day and is divided into parts of from 1 to 3000 mg each to be administered to patients several times a day.

Where the stilbene derivatives of the present invention are formulated into peroral preparations, a vehicle and optionally other additives such as binder, disintegrator, lubricant, colorant, flavoring, etc. are added thereto and the resulting mixtures are formed into tablets, coated tablets, granules, capsules, etc. by ordinary methods. As the vehicle, for example, usable are lactose, corn starch, white sugar, glucose, sorbitol, crystalline cellulose, etc. As the binder, for example, usable are polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, arabic gum, tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropyl starch, polyvinyl pyrrolidone, etc. As the disintegrator, for example, usable are starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextran, pectin, etc. As the lubricant, for example, usable are magnesium stearate, talc, polyethylene glycol, silica, hardened vegetable oils, etc. As the colorant, for example, usable are colorants that have been accepted as those applicable to medicines. As the flavoring, for example, usable are cocoa powder, menthol, 'aromatic acids, peppermint oil, borneol, cinnamon powder, etc. As a matter of course, these tablets and granules may optionally be coated, for example, with sugar coats, gelatin coats, etc.

Where the stilbene derivatives of the present invention are formulated into injections, a pH-adjusting agent, a buffer, a stabilizer, a preservative, etc. may optionally be added thereto and formed into subcutaneous, intramuscular or intravenous injections by ordinary methods.

The stilbene derivatives of the present invention may optionally be formed into their pharmaceutically-acceptable acid-addition salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, etc. and with organic acids such as oxalic acid, fumaric acid, maleic acid, malic acid, citric acid, tartaric acid, glutamic acid, etc.

Examples

The present invention will be explained in detail by means of the following examples, which, however, are not intended to restrict the scope of the present invention.

Example 1:

Preparation of (Z)-1-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

Step 1:

Preparation of (Z)-1-(3-nitro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

1.54 g of 3-nitro-4-methoxybenzaldehyde and 4.45 g of 3,4,5-trimethoxybenzyltriphenylphosphine bromide were dissolved in 40 ml of benzene, and a benzene solution containing 408 mg of sodium hydride dispersed therein was added thereto and reacted for 15 hours at room temperature. The reaction mixture was neutralized with acetic acid, saturated saline solution was added thereto, and the resulting liquid was extracted with dichloromethane. The extract was dried with anhydrous sodium sulfate, concentrated and then purified by silica gel column chromatography (ethyl acetate:hexane = 1:2) to obtain 1.27 g of the intended compound. The yield of the product was 43 %.

^{1}H-NMR($CDCl_3$):7.79(1H, d, J=2.1), 7.42(1H ,dd ,J=2.1 ,8.7), 6.93(1H, d, J=8.7), 6.58(1H, d, J=12.9), 6.47(2H, s), 6.44(1H, d, J=12.9), 3.93(3H, s), 3.85(3H, s), 3.71(6H ,s); mass spectrum (m/z):345(M^+)

Step 2:

Production of (Z)-1-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

700 mg of (Z)-1-(3-nitro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene were dissolved in 35 ml of acetic acid, and 7 g of zinc were added thereto and stirred for one hour. The reaction liquid was filtered, concentrated and purified by silica gel column chromatography (dichloromethane:hexane = 2:1) to obtain 314 mg of the intended compound. Its yield was 49.3 %.

^{1}H-NMR($CDCl_3$):6.69(1H, s), 6.67(2H, s), 6.55(2H, s),6.45(1H, d, J=12.0), 6.36(1H, d, J=12.0), 3.84(3H, s), 3.82(3H, s), 3.69(6H, s); mass specturm (m/z):315(M^+)

Example 2:

Production of (Z)-1-(3-amino-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

Step 1:

Production of (Z)-1-(3-nitro-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

1.0 g of 3-nitro-4-chlorobenzaldehyde and 2.8 g of 3,4,5-trimethoxybenzyltriphenylphosphine bromide were dissolved in 50 ml of benzene, and a benzene solution containing 260 mg of sodium hydride dispersed therein was added thereto and reacted for 15 hours at room temperature. The reaction liquid was neutralized with acetic acid, saturated saline solution was added thereto, and the resulting liquid was

extracted with dichloromethane. The extract was dried with anhydrous sodium sulfate, concentrated and then purified by silica gel column chromatography (ether:hexane = 1:2) to obtain 0.95 g of the intended compound. The yield of the product was 50.4 %.

^{1}H-NMR($CDCl_3$):7.79(1H, s), 7.39(2H, s), 6.70(1H, d, J=12.0), 6.47(1H, d, J=12.0), 6.44(2H, s), 3.86(3H, s), 3.72(6H, s); mass spectrum (m/z):349(M^+)

Step 2:

Production of (Z)-1-(3-amino-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

85 mg of (Z)-1-(3-nitro-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene were dissolved in 4 ml of acetic acid and 4 ml of dichloromethane, and 400 mg of zinc were added thereto and stirred for one hour. The reaction liquid was filtered, concentrated and purified by silica gel column chromatography (dichloromethane:hexane = 2:1) to obtain 52 mg of the intended compound. Its yield was 66.8 %..

^{1}H-NMR($CDCl_3$):7.12(1H, d, J=7.8), 6.71(1H, d, J=1.8), 6.62(1H, d, j=1.8, 7.8), 6.49(2H, s), 6.45(2H, s), 3.84(3H, s), 3.69(6H, s); mass specturm (m/z):319(M^+)

Example 3:

Production of (Z)-1-(3-amino-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

Step 1:

Production of (Z)-1-(3-nitro-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

1.0 g of 3-nitro-4-methylbenzaldehyde and 3.3 g of 3,4,5-trimethoxybenzyltriphenylphosphine bromide were dissolved in 50 ml of benzene, and a benzene solution containing 302 mg of sodium hydride dispersed therein was added thereto and reacted for 15 hours at room temperature. The reaction liquid was neutralized with acetic acid, saturated saline solution was added thereto, and the resulting liquid was extracted with dichloromethane. The extract was dried with anhydrous sodium sulfate, concentrated and then purified by silica gel column chromatography (ether:hexane = 1:2) to obtain 0.99 g of the intended compound. The yield of the product was 47.8 %.

^{1}H-NMR($CDCl_3$):7.89(1H, d, J=1.8), 7.40(1H, dd, J=1.8, 7.8), 7.19(1H, d, J=7.8), 6.63(1H, d, J=12.3), 6.50(1H, d, J=12.3), 6.46(2H, s), 3.85(3H, s), 3.69(6H, s), 2.55(3H, s); mass spectum (m/z):329(M^+)

Step 2:

Production of (Z)-1-(3-amino-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene:

65 mg of (Z)-1-(3-nitro-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene were dissolved in 4 ml of acetic acid and 4 ml of dichloromethane, and 300 mg of zinc were added thereto and stirred for one hour. The reaction liquid was filtered, concentrated and purified by silica gel column chromatography (dichloromethane:hexane = 2:1) to obtain 29 mg of the intended compound. Its yield was 46.5 %.

^{1}H-NMR($CDCl_3$):6.93(1H, d, J=7.5), 6.65(1H, dd, J=1.8, 7.5), 6.63(1H, d, J=1.8), 6.53(2H, s), 6.49(1H, d, J=12.3), 6.40(1H, d, J=12.3), 3.83(3H, s), 3.68(6H, s), 2.13(3H, s); mass spectrum (m/z):299(M^+)

Example 4:

Production of (E)-3-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

Step 1:

Production of (Z)-3-(3-nitro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

3.0 g of 3-nitro-4-methoxybenzaldehyde, 3.4 g of 3,4,5-trimethoxyphenylacetonitrile, 800 mg of sodium hydroxide and 100 mg of octylmethylammonium chloride were dissolved in 15 ml of water and 15 ml of dichloromethane and reacted for 4 hours at room temperature. Ice water was added to the reaction liquid, which was then extracted three times each with dichloromethane. The extract was dried with anhydrous sodium sulfate and concentrated. The concentrated liquid was purified by crystallization (ethyl acetate) to obtain 4.4 g of the intended compound. Its yield was 72 %.

^{1}H-NMR($CDCl_3$):8.30(1H, dd, J=2.4, J=9.0), 8.21(1H, d, J=2.4), 7.38(1H, s), 7.21(1H, d, J=9.0), 6.86(2H, s), 4.05(3H, s), 3.94(6H, s), 3.89(3H, s); mass spectrum (m/z):370(M^+); melting point 191-192°C

Step 2:

Production of (E)-3-(3-nitro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

2.0 g of (Z)-3-(3-nitro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile were dissolved in 500 ml of acetonitrile and exposed to visible light rays for 60 minutes. The reaction liquid was concentrated and crystallized from ethyl acetate to obtain 996 mg of the intended compound. Its yield was 49 %.

^{1}H-NMR($CDCl_3$):7.74(1H, d, J=2.1), 7.35(1H, dd, J=2.1, 9.0), 7.19(1H, s), 6.94(1H, d, J=9.0), 6.58(2H, s), 3.95(3H, s), 3.89(3H, s), 3.78(6H, s); mass spectrum (m/z):370(M^+); melting point 158-159°C

Step 3:

Production of (E)-3-(3-amino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

500 mg of (E)-3-(3-nitro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile were dissolved in 25 ml of acetic acid, and 5 g of zinc were added thereto and stirred for 30 minutes at room temperature. The reaction liquid was filtered and then concentrated. The concentrated liquid was purified by silica gel column chromatography (ethyl acetate:hexane = 1:2) to obtain 457 mg of the intended compound. Its yield was 99 %.

^{1}H-NMR($CDCl_3$):7.26(1H, s), 7.16(1H, s), 6.65(2H, s), 6.64(1H, s), 6.56(1H, s), 3.88(3H, s), 3.84(3H, s), 3.77(6H, s); mass spectrum (m/z):340(M^+); melting point 144-145°C

Example 5:

Production of (E)-3-(3-amino-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

Step 1:

Synthesis of (Z)-3-(3-nitro-4-methylphenyl)- 2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

5.0g of 3-nitro-4-methylbenzaldehyde, 6.27 g of 3,4,5-trimethoxyphenylacetonitrile, 1.44 g of sodium hydroxide and 500 mg of trioctylmethylammonium chloride were dissolved in 25 ml of water and 500ml of dichloromethane. The mixture was stirred vigorously for 3 hours at room temperature. Then ice water was added to the mixture and the mixture was extracted with dichloromethane three times and dried 'over anhydrous sodium sulfate. Organic layer was concentrated and the residue was purified by silicagel column chromatography (dichloromethane) to give 1.5 g of the intended compound. Its yield was 14.1%.

^{1}H-NMR($CDCl_3$):8.35(1H, J=1.5), 8.18(lH, dd, J=1.5,8.1), 7.47(1H, d, J=8.1), 7.44(1H, s), 6.88(2H, s), 3.95(6H, s), 3.90(3H, s), 2.67(3H, s); mass spectrum (m/z):354(M^+); melting point 162-163°C

Step 2:

Synthesis of (E)-3-(3-nitro-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

1.38 g of (Z)-3-(3-nitro-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile was dissolved in 500 ml of acetone and the mixture was reacted in photochemical apparatus (visible light) for 1 hour. The reaction mixture was concentrated and a quarter of it was purified by silica gel plate to give 100 mg of the intended compound.

^{1}H-NMR($CDCl_3$):7.84(1H, d, J=1.8), 7.29(1H, dd, J=1.8, 8.1), 7.26(1H, s), 7.22(1H, d, J=8.1), 6.56(2H, s), 3.89(3H, s), 3.75(3H, s), 2.57(3H, s); mass spectrum(m/z):354(M^+); melting point:169-170°C

Step 3:

Synthesis of (E)-3-(3-amino-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-ene-nitrile:

84 mg of(E)-3-(3-nitro-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile was dissolved in 8 ml of acetic acid then zinc was added to the mixture. The- mixture was stirred vigorously for 1 hour then filtrated and concentrated. The residue was purified by silica gel plate (dichloromethane) to give 60 mg of the intended compound.

^{1}H-NMR($CDCl_3$):7.20(1H, s), 6.92(1H, d, J=7.5), 6.62(2H, s), 6.56(1H, dd, J=0.9, 7.5), 6.51(1H, s), 3.87(3H, s), 3.75(6H, s), 2.13(3H, s); mass spectrum (m/z):324(M^+); melting point:161-162°C

Example 6

Synthesis of (E)-3-(3-amino-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-ene-nitrile:

Step 1

Synthesis of (Z)-3-(3-nitro-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile

5.0 g of 3-nitro-4-chlorobenzaldehyde, 5.6 g of3,4,5-trimethoxyphenylacetonitrile, 1.3 g of sodium hydroxide and 500 mg of trioctylmethylammonium chloride were dissolved in 10ml of water and 50ml of dichloromethane. The mixture was stirred vigorosly for 3 hour at room temperature. Then ice water was added to the mixture and the mixture was extracted with dichloromethane three times and dried over anhydrous sodium sulfate. Organic layer was concentrated and the residue was crystalized from ethyl acetate to give 4.9 g of the intended compound. Its yield was 48.5%.

^{1}H-NMR($CDCl_3$):8.23(1H, J=2.1), 8.15(1H, dd, J=2.1, 8.4), 7.67(1H, d, J=8.4), 7.41(1H, s), 6.88(2H, s), 3.94(6H, s), 3.91(3H, s); mass spectrum (m/z):374(M^+); melting point:198-199°C

Step 2

Synthesis of (E)-3-(3-nitro-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)prop-2-ene-nitrile:

1.5 g of (Z)-3-(3-nitro-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile was dissolved in 500 ml of acetone and the solution was reacted in photochemical apparatus (visible light) for 1 hour. The reaction mixture was concentrated and a half of it was purified by silica gel plate to give 400 mg of the

intended compound.

^{1}H-NMR($CDCl_3$):7.74(1H, d, J=2.1), 7.44(1H, d, J=8.7), 7.32(1H, dd, J=2.1, 8.7), 7.23(1H, s), 6.55(2H, s), 3.89(3H, s), 3.77(6H, s); mass spectrum (m/z):374(M^+)

Step 3:

Synthesis of (E)-3-(3-amino-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile:

(E)-3-(3-nitro-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)-prop-2-ene-nitrile 330 mg was dissolved in 8 ml of acetic acid then zinc was added to the mixture. The mixture was stirred vigorously for 1h then filtered and concentrated. The residue was purified by silica gel plate (dichloromethane) to give 102 mg of desired product (yield 33%).

^{1}H-NMR($CDCl_3$):7.17(1H, s), 7.12(1H, d, J=8.1), 6.61(1H, d, J=1.8), 6.59(2H, s), 6.53(1H, dd, J=1.8, 8.1), 3.88(3H, s), 3.75(6H, s); mass spectrum:344(M^+); melting point:150-151°C

Example 7:

Cytotoxicity test:

Mouse P388 leukemia cells were used as cancer cells for the test. The cancer cells were incubated in RPMI-1640 medium containing 5 μM 2-mercaptoethanol and 10 % fetal calf serum. Precisely, the cancer cells were seeded in a 96-well microplate in an amount of 1 x 10^4 cell/50 μl/well, 25 μl/well of an aqueous solution of the test compound mentioned below (4 μg/ml) were added to each well, and the cells were incubated therein for 2 days at 37 °C. After the incubation, the number of the living cells was counted by MTT method and a dose-reaction curve was formed from the counted data. Based on the curve, the 50 % growth-inhibiting concentration (IC_{50}) of the test compound was calculated. The IC_{50} value of each compound is shown in Table 1. As a comparative compound, Combretastatin A-4 was used. As is noted from Table 1, the compounds of the present invention each have IC_{50} value comparable to that of Combretastatin A-4.

Example 8:

Evaluation of Antitumor Activity:

Colon 26 was inoculated sc into CD2F1 mice. After a week, the size of tumor was measured and the volume of the tumor was calculated. Mice were selected on the volume of the tumor and administration of drug was began. After 21 days from the day of administration, the size of the tumor was measured and the volume of tumor was calculated. I.R.(Inhibition ratio of growth of tumor) was calculated as below.

I.R.(%) = {1 - (average tumor volume of treated mice)/(average tumor volume ofcontrol mice)}x100

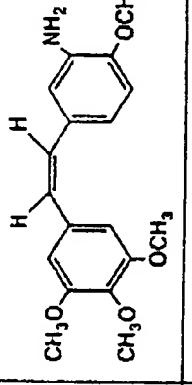
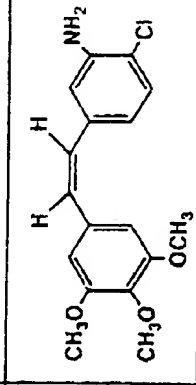
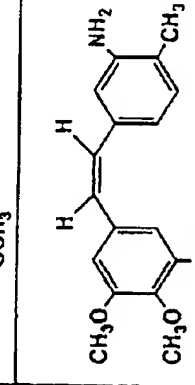
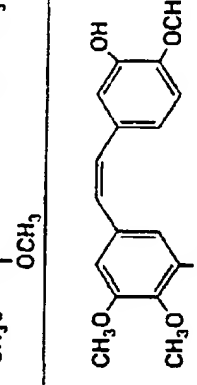
The inhibition ratios are shown in Table 1.

Example 9:

Solubility:

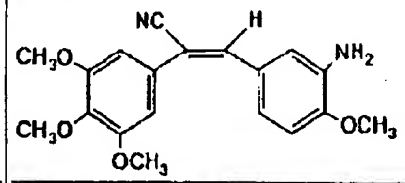
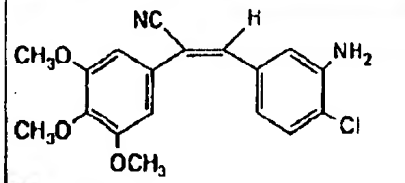
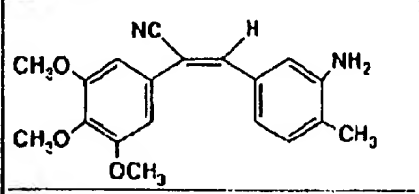
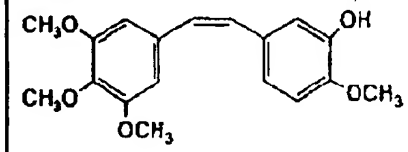
Excess amount of each sample was dissolved in 0.1ml of phosphate buffer (PH 7.0). The mixture was sonicated and centrifuged. The supernatant was subjected to HPLC and the solubility was measured. Results are shown in Table 2.

TABLE 1

NAME OF COMPOUNDS	STRUCTURE	In vitro IC_{50} (ng/ml)	In vivo I.R. (%)
(Z)-1-(3-Amino-4-methoxy phenyl)-2-(3,4,5-trimethoxy phenyl)-ethene		0.2	69.5 [a), c)] (40mg/day)
(Z)-1-(3-Amino-4-chloro phenyl)-2-(3,4,5-trimethoxy phenyl)-ethene		20	NOT TESTED
(Z)-1-(3-Amino-4-methyl phenyl)-2-(3,4,5-trimethoxy phenyl)-ethene		3.5	61.6 [a), c)] (40mg/day)
Combretastatin A-4		0.2	4.6 [a), d)] (40mg/day)

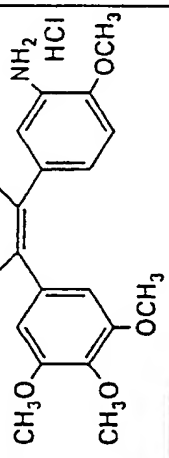
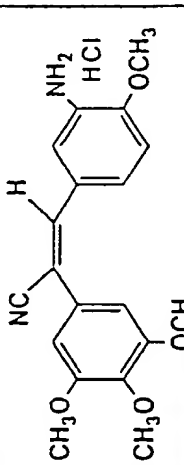
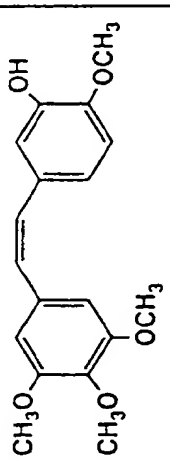
Administration
a) compounds were given once on day1, day5 and day7
b) compounds were given once daily from day1 to day 10
c) compounds were given iv
d) compounds were given po

TABLE 1 CONTINUED

NAME OF COMPOUNDS	STRUCTURE	In vitro IC_{50}(ng/ml)	In vivo I.R. (%)
(E)-3-(3-Amino-4-methoxy phenyl)-2-(3,4,5-trimethoxy phenyl)-prop-2-enenitrile		0.2	83.4 [b),c)] (10mg/day)
(E)-3-(3-Amino-4-chloro phenyl)-2-(3,4,5-trimethoxy phenyl)-prop-2-enenitrile		1.8	23.7 [a),d)] (80mg/day)
(E)-3-(3-Amino-4-methyl phenyl)-2-(3,4,5-trimethoxy phenyl)-prop-2-enenitrile		2.0	41.0 [a), d)] (40mg/day)
Combretastatin A-4		0.2	4.6 [a), d)] (40mg/day)

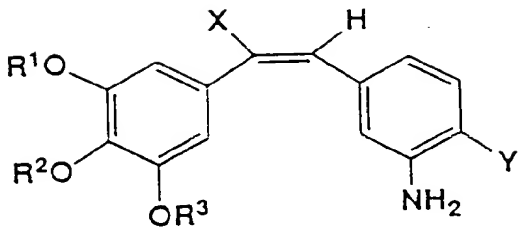
Administration
a) compounds were given once on day1, day5 and day7
b) compounds were given once daily from day1 to day 10
c) compounds were given iv
d) compounds were given po

TABLE 2

NAME OF COMPOUNDS	STRUCTURE	Solubility In Phosphate Buffer (PH 7.0)(mg/ml)
(Z)-1-(3-Amino-4-methoxy phenyl)-2-(3,4,5-trimethoxy phenyl)-ethene		3.4
(E)-3-(3-Amino-4-methoxy phenyl)-2-(3,4,5-trimethoxy phenyl)-prop-2-enenitrile		1.7
Combretastatin A-4		<0.1

Claims

1. A stilbene derivative of general formula (1) or a pharmaceutically acceptable acid addition salt thereof:



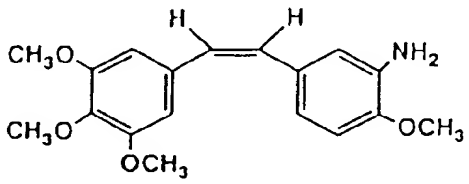
(1)

wherein R^1, R^2 and R^3 each represent an alkyl group having 1 to 3 carbon atoms; X represents a hydrogen atom or a nitrile group; Y represents an alkyloxy group having 1 to 3 carbon atoms, an alkyl group having 1 to 6 carbon atoms or a halogen atom.

2. A stilbene derivative or pharmaceutically acceptable acid addition salt thereof according to claim 1 in which R^1, R^2 and R^3 are all methyl.

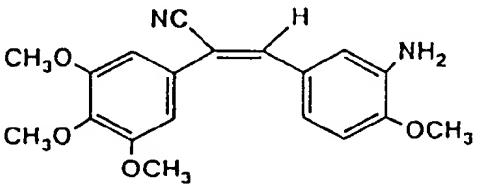
3. A stilbene derivative or pharmaceutically acceptable acid addition salt thereof according to claim 1 or claim 2 wherein Y is a methoxy group.

4. A compound according to claim 1 having the formula



or a pharmaceutically acceptable acid addition salt thereof.

5. A compound according to claim 1 having the formula

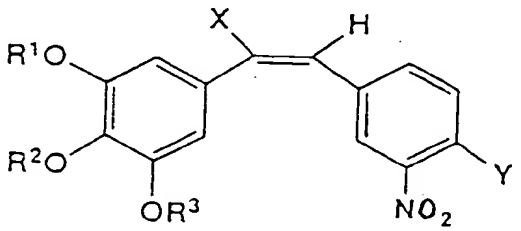


6. A compound according to any one of the preceding claims for pharmaceutical use.

7. A carcinostatic composition comprising a compound of any one of claims 1 to 5 and a pharmaceutically acceptable excipient, diluent, or carrier.

8. Use of a compound of any one of claims 1 to 5 in the manufacture of a carcinostatic.

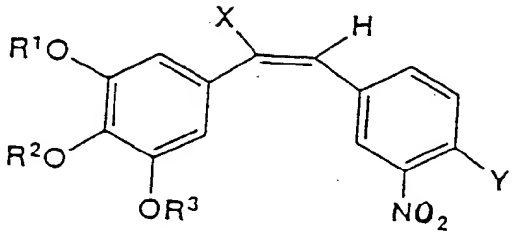
9. A method for the production of a compound of formula (1) as defined in claim 1, comprising reduction of a compound of formula (1A)



(1A)

wherein R^1, R^2, R^3, X and Y are as defined in claim 1.

10. A compound of formula (1A)



(1A)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 6522

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A,D	JOURNAL OF MEDICINAL CHEMISTRY, vol.34, no.8, 1991, WASHINGTON US pages 2579 - 2588 M. CUSHMAN ET AL. 'Synthesis and Evaluation of Stilbene and Dihydrostilbene Derivatives as Potential Anticancer Agents that Inhibit Tubulin Polymerization' * the whole document; see especially table I, compound 5n; table II, compounds 6n, 6z; table III, compounds 8n, 8z * ---	1-8	C07C217/84 C07C217/80 C07C255/43 A61K31/135 A61K31/275
A,D	JOURNAL OF MEDICINAL CHEMISTRY, vol.35, no.12, 1992, WASHINGTON US pages 2293 - 2306 M. CUSHMAN ET AL 'Synthesis and Evaluation of Analogues of (Z)-1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene as Potential cytotoxic and antimitotic Agents' * the whole document * ---	1-8	
A	CHEMICAL ABSTRACTS, vol. 79, no. 3, 23 July 1973, Columbus, Ohio, US; abstract no. 13526, J. CH. DORE, C. VIEL page 21 ; * abstract * & J. PHARM. BELG., vol.28, no.1, 1973 --- -/--	1-8	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	7 December 1994	SEUFERT, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EUROPEAN SEARCH REPORT

Application Number
EP 94 30 6522

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	JOURNAL OF MEDICINAL CHEMISTRY, vol.27, no.5, 1984, WASHINGTON US pages 577 - 585 R. W. HARTMANN ET AL. 'Ring-Substituted 1,2-Dialkylated 1,2-Bis(hydroxyphenyl)ethanes. 2. Synthesis and Estrogen Receptor Binding Affinity of 4-4'-5,5', and 6,6'-Disubstituted Metahexestrols' * page 577, left column, line 1 - line 9; examples 12,13 *	1-8	
A	JOURNAL OF PHARMACEUTICAL SCIENCES, vol.60, no.8, 1971, WASHINGTON US pages 1244 - 1245 J. T. STEWART 'Synthesis and Biological Evaluation of substituted .alpha.-Phenylcinnamonitriles' * page 1244, right column, last paragraph - page 1245, left column, paragraph 1; example 9 *	1,9	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
P,X, D	WO-A-93 23357 (RESEARCH CORPORATION TECHNOLOGIES) * page 3, line 1 - page 5, line 5 *	1-8	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	7 December 1994	SEUFERT, G

CATEGORY OF CITED DOCUMENTS

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